Remarks

Upon entry of the foregoing amendment, claims 1, 11, 17, 19, 22-25, 30-39, and 44-58 are pending in the application, with claims 1, 11, 17, 19, and 22-24 withdrawn from consideration. Claims 2-10, 12-16, 18, 20-21, 26-29, and 40-43 have been canceled without prejudice or disclaimer. Applicants reserve the right to pursue the subject matter of claims 2-10, 12-16, 18, 20-21, 26-29, and 40-43 in related applications. Claims 25 and 39, and dependent claims 30-33 and 35-38 were amended to clarify the claimed invention in light of the final restriction requirement of the present office action, Paper No. 8. No new matter has been added.

I. Claim Objections:

On page 4, lines 9-12 of Paper No. 8, the Examiner states, "Claims 26 and 40 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form." Claims 26 and 40 have been canceled thereby obviating this rejection.

On page 4, lines 15 to page 5, line 1 of Paper No. 8, the Examiner states, "Claims 38 and 55 are objected to because of the following informalities: Claims 38 and 55 recite a hybridoma that produces the antibody or fragment thereof. Hybridomas are known to produce antibodies not fragments of antibodies. Applicant is required to amend the claims so that it would not read on fragments of antibodies are produced by hybridomas. The Examiner suggest that Applicant insert -produced from the antibody" therefor "thereof" in line 1 of the claims to obviate the rejection."

Applicants comprehend the Examiner's objection to claims 38 and 55, however Applicants do not comprehend the Examiner's suggested changes to the claim. Nevertheless, Applicants have amended claims 38 and 55 to remove the phrase "or fragment thereof," thereby obviating the objection.

II. Amendments to the Specification:

On page 5, lines 4-6 of Paper No. 8, the Examiner states, "The disclosure is objected to because of the following informalities: The text of the specification refers to a Table 1. Such table cannot be found within the specification." Applicants respectfully point out that

Table 1 appears on pages 93-97 of the specification as filed, and a detailed explanation of the columns in Table 1 is given on pages 98-99. However, to more clearly identify the table on pages 93-97 as Table 1, Applicants have amended the specification to insert a "Table 1" at the top of pages 93-97. No new matter has been added with this amendment.

III. Rejections under 35 U.S.C. § 101/§ 112:

The Examiner has rejected claims 25-26, 30-40 and 44-58 under 35 U.S.C. § 101, because the claimed invention is allegedly not supported by either a specific and substantial asserted utility or a well established utility. See, Paper No. 8, page 5. More particularly, the Examiner states the following at page 6, line 2 of Paper No. 8:

> The applicant has not disclosed the specific activity of the protein having amino acid sequence of SEQ ID NO. 125. The disclosure that Applicant does provide is a list of speculative uses of the protein, such as diagnosis and/or treatment of osteoclastoma, treating diseases of the musclulo-skeletal system and cardiac diseases; to determine bio-activity, raise antibodies; and as tissue markers which are not specific and substantial utilities. Applicant has not provided any evidence that conveys the linkage between the level of expression of the protein and osteoclastoma. Without such evidence it is unclear how the protein can be utilized in the diagnosis of osteoclastoma, particularly in view of the protein's expression in other tissues. Thus, the utility of the protein is not specific and substantial. Without a specific and substantial asserted utility for the protein, the isolated antibody that binds to the protein having SEQ. ID. NO. 125 also lacks specific and substantial utility. Therefore, the claimed invention is rejected under 35 U.S.C § 101 for lacking support for a specific and substantial utility for the isolated antibody.

Applicants respectfully disagree and traverse this rejection.

A. On page 6, lines 2-4, of Paper No. 8, the Examiner alleges that, "The applicant has not disclosed the specific activity of the protein having amino acid sequence of SEQ ID NO. 125," and that "The disclosure that Applicant does provide is a list of speculative uses of the protein...."

Applicants respectfully point out that there is no requirement under 35 U.S.C. § 101 that an inventor teach the scientific principle of the invention nor are Applicants aware of any requirement that an applicant describe the "specific activity" of a polypeptide before said polypeptide is deemed to satisfy the utility requirements under 35 U.S.C. § 101. Applicants

need only make one credible assertion of specific utility for the claimed invention to satisfy 35 U.S.C. §101 and 35 U.S.C. §112; additional statements of utility, even if not "credible," do not render the claimed invention lacking in utility. *See, e.g., Raytheon v. Roper*, 220 U.S.P.Q. 592, 598 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 835 (1984) ("When a properly claimed invention meets at least one stated objective, utility under 35 U.S.C. §101 is clearly shown.").

Moreover, there is nothing improper about reciting multiple utilities for an invention. Indeed, the M.P.E.P. at § 2107.02 states "[i]t is common and sensible for an applicant to identify several specific utilities for an invention . . .". Further, "[i]f applicant makes one credible assertion of utility, utility for the claimed invention as a whole is established." *Id.* *See also, In re* Malachowski, 189 U.S.P.Q. 432 (C.C.P.A. 1976); Hoffman v. Klaus, 9 U.S.P.Q.2d 1657 (Bd. Pat. App. & Inter. 1988). Thus, the Examiner's contention that, "The disclosure that Applicant does provide is a list of speculative uses of the protein..." is improper and immaterial.

B. On page 6, lines 4-7, of Paper No. 8, the Examiner alleges that, "...uses of the protein, such as diagnosis and/or treatment of osteoclastoma, treating diseases of the musclulo-skeletal system and cardiac diseases; to determine bio-activity, raise antibodies; and as tissue markers which are not specific and substantial utilities."

Applicants respectfully submit that the use of the polypeptide of this invention for the diagnosis of skeletal disorders, such as osteoclastoma is a credible assertion of and specific utility.

First, Applicants submit that the present specification **discloses a biological activity**, and **reasonably correlates that activity to a disease or condition**, thereby sufficiently identifying a **specific utility** for the invention. *See* M.P.E.P. § 2107.01 at 2100-32 (paraphrased). Stated in other words, so long as the correlation between the biological activity and the asserted use in a particular disease or condition is sufficient to convince one of skill in the art, then the specificity requirement of 35 U.S.C. § 101 is satisfied. *See also,* Fujikawa v. Wattanasin, 39 U.S.P.Q.2d 1895 (Fed. Cir. 1996). Applicants submit that the following passage from the present specification readily satisfies the specificity requirement of 35 U.S.C. § 101:

> This gene is expressed primarily in osteoclastoma and brain tissues. Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s)

> present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neural or skeletal disorders, particularly osteoclastoma.

See page 57, lines 22-26.

Thus, the specification supports a specific use for the disclosed polypeptide: to diagnose skeletal disorders, such as osteoclastoma.

Moreover, **this asserted utility is also substantial**, as measurement "...of the presence of a material (e.g., detection of the HCE5F43 polypeptide of this invention with the claimed antibodies) which has a stated correlation to a predisposition to the onset of a particular disease condition (e.g., skeletal disorders, such as osteoclastoma) would also define a "real world" context of use...." *See* M.P.E.P. § 2107 at 2100-32.

In addition, pharmacological or therapeutic inventions that provide any "immediate benefit to the public" satisfy 35 U.S.C. § 101. *See*, Nelson v. Bowler, 626 F.2d 853, 856, 206 U.S.P.Q. 881, 883 (C.C.P.A. 1980); *See also,* M.P.E.P. §2107.01(III). The diagnosis of osteoclastoma is certainly of public benefit.

C. On page 6, lines 7-10, of Paper No. 8, the Examiner alleges that, "Applicant has not provided any evidence that conveys the linkage between the level of expression of the protein and osteoclastoma. Without such evidence it is unclear how the protein can be utilized in the diagnosis of osteoclastoma, particularly in view of the protein's expression in other tissues."

Applicant's respectfully point out that the linkage between the level of expression and osteoclastoma is disclosed in stating that the gene is "primarily expressed in osteoclastoma." Moreover, Applicant's specification clearly states how expression of the polypeptide of this invention relates to diagnosis of skeletal disease, such as osteoclastoma:

> Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune and central nervous system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., neural, skeletal, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

See page 57, lines 26-34 of the present specification.

Contrary to the Examiner's contention that, "...it is unclear how the protein can be utilized in the diagnosis of osteoclastoma, particularly in view of the protein's expression in other tissues," Applicants respectfully submit that the polypeptide of this invention **can be utilized in the diagnosis of osteoclastoma regardless of the its expression in other tissues**. In fact, the primary way to diagnose an osteoclastoma is through biopsy, as stated in the following text book of Orthopaedics and Traumatology:

> Biopsy is the most crucial procedure in the diagnosis of musculo skeletal lesions. The appropriate treatment cannot be initiated until the correct tissue diagnosis is available.

See Exhibit A, page 6, *The Madras Bone Tumor Service.* http://www.bonetumour.org/HTMLS/text_book_all; chapter 9 – tumours of bone (January 5, 2004): An online excerpt from "Text Book of Orthopaedics and Traumatology" Fifth Edition, February 2002. M.Natarajan, Ph.D., Emeritus Professor of Orthopaedic Surgery, 276 Pages, M.N.Orthopaedic Hospital publishers.

Moreover, there is an important, yet unmet need for accurate diagnosis of skeletal tumors, such as osteoclastomas:

> One must remember that clinically, certain non neoplastic lesions present as swellings in the bone simulating a tumour e.g. Solitary bone cyst, fibrous dysplasia, Brown tumour lesion in Hyperparathyroidsm, etc.
>
> Thus, the diagnosis of bone tumour can be often very difficult. Accurate diagnosis is very important as a mistaken diagnosis of a malignant bone tumour can lead to a very unfortunate result like an unnecessary amputation of the limb.

See Exhibit A, page 2, *The Madras Bone Tumor Service.* http://www.bonetumour.org/HTMLS/text_book_all; chapter 9 – tumours of bone (January 5, 2004): An online excerpt from "Text Book of Orthopaedics and Traumatology" Fifth Edition, February 2002. M.Natarajan, Ph.D., Emeritus Professor of Orthopaedic Surgery, 276 Pages, M.N.Orthopaedic Hospital publishers.

Thus, detection of the expression of a molecular marker, such as the polypeptide of this invention, in a skeletal disesase, such as osteoclastoma, has specific and substantial, and credible utility. Applicants submit that since the polypeptide of this invention has a specific and substantial, and credible utility the antibody that binds to the polypeptide of this invention also has a specific and substantial utility, namely to detect the polypeptide of this invention in

skeletal disease, for example osteoclastoma. Accordingly, Applicants respectfully request that rejection of claims 25-26, 30-40, and 44-58 under 35 U.S.C. § 101, first paragraph, be reconsidered and withdrawn.

On page 6, lines 16 to page 7, lines 2, the Examiner states that claims 25-26, 30-40, and 44-58 are also rejected under 35 U.S.C. § 112, first paragraph, for the following reason:

> "Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to make and use the claimed invention."

As discussed above in response to the rejection under 35 U.S.C. § 101, the claimed invention is supported by a specific, substantial and credible asserted utility. The Examiner "should not impose a 35 U.S.C. § 112, first paragraph, rejection grounded on a 'lack of utility' basis unless a 35 U.S.C. §101 rejection is proper." M.P.E.P. § 2107 (IV) at 2100-36. Therefore, because the polypeptide of this invention complies with the utility requirement of 35 U.S.C. § 101, the rejections under 35 U.S.C. § 112, first paragraph, based on the alleged lack of utility of the claimed antibodies, should be withdrawn. Accordingly, Applicants respectfully request that the rejection of claims 25-26, 30-40, and 44-58 under 35 U.S.C. § 112, first paragraph, be reconsidered and withdrawn.

IV. <u>Rejections under 35 U.S.C. § 112, first paragraph</u>

In Paper No. 8, page 7, lines 9-13, the Examiner rejects claims 25-26, 30-40, and 44-58 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. More specifically, the examiner states, "The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention."

Applicants respectfully traverse and request that the rejection be withdrawn for the reasons explained *infra*. In support of the enablement rejection, the Office Action refers to eight factors set forth in *Ex Parte Forman* (230 U.S.P.Q. 546 (1986)) that are to be considered in determining whether or not a specification is sufficiently enabling without undue experimentation. Applicants assert, however, that in contrast to the situation in *Ex Parte Forman*, the specification in the present case <u>is</u> sufficiently enabling to one having ordinary skill in the relevant field. Moreover, the present case is closely analogous to the situation

presented and decided upon in *In Re Wands* (where the court affirmed and opined upon the eight considerations iterated in *Ex Parte Forman). See, In re Wands,* 858 F.2d 731 (1988). In this regard, the M.P.E.P. has also explicitly incorporated the decision in *In Re Wands* as part of the guidelines to be utilized in considering enablement issues:

> *In re Wands,* 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (reversing the PTO's determination that claims directed to methods for detection of hepatitis B surface antigens did not satisfy the enablement requirement). In *Wands*, the court noted that there was no disagreement as to the facts, but merely a disagreement as to the interpretation of the data and the conclusion to be made from the facts. *In re Wands,* 858 F.2d at 736-40, 8 USPQ2d at 1403-07. The Court held that the specification was enabling with respect to the claims at issue and found that "there was considerable direction and guidance" in the specification; there was "a high level of skill in the art at the time the application was filed;" and "all of the methods needed to practice the invention were well known." 858 F.2d at 740, 8 USPQ2d at 1406. After considering all the factors related to the enablement issue, the court concluded that "it would not require undue experimentation to obtain antibodies needed to practice the claimed invention." *Id.*, 8 USPQ2d at 1407.

M.P.E.P., 8th Ed., § 2164.01(a) (Aug. 2001, *revised* Feb. 2003) (emphasis added).

The present application presents a situation very much like that considered in *In Re Wands* where the specification was found enabling for the claimed antibodies because of the considerable direction and guidance in the specification, the high level of skill in the art, and the well-established methods needed to practice the invention. As discussed below, the present specification does, like *In Re Wands*, provide more than ample guidance to those of ordinary skill in the art for how to make and use the claimed antibodies and methods based thereon.

As of the earliest priority date for the present application, methods for making and using a diverse array of antibody types (*e.g.* monoclonal, single-chain, Fab fragments, etc.) were routine for those of ordinary skill in the art. *See e.g.*, specification, page 107, lines 20-27. In this regard, the specification describes various types of antibodies that may be produced against the polypeptide of this invention (*e.g.*, polyclonal, monoclonal, single chain, chimeric, humanized, etc.), how these antibodies may be produced, and directs the reader to instructional resources for the same. *See* "Example 10: Production of an antibody from a polypeptide" on pages 137-138. The specification also describes and details examples of assays that make use of the claimed antibody, such as radioimmunoassays, competitive-

binding assays, Western blot analysis, ELISA assays, and "sandwich" assays. *See*, specification, 113, line 6 to page 114, line 19.

The particular use of the antibody of this invention to differentiate diseased from normal tissue via specific binding of the antibody to a particular polypeptide is described on page 113, lines 37-41, as well as in "Example 22: Method of Detecting Abnormal Levels of a Polypeptide in a Biological Sample" page 153, line 31 to page 154, line 14. The specification even describes how antibodies may be used to carry out *in vivo* imaging to detect a diseased state of colon tissue. *See*, specification at page, 113, lines 25-36. Hence, Applicants submit that the present application provided sufficiently ample guidance as of its original filing date in teaching how to make and use the presently claimed antibodies and methods based thereon. Thus, the specification fully enables one of skill in the art to make the claimed antibodies and use the claimed antibodies to detect skeletal disease, such as osteoclastoma, without undue experimentation. Accordingly, Applicants respectfully request that the rejection of claims 25-26, 30-40, and 44-58 under 35 U.S.C. 112, first paragraph be reconsidered and withdrawn.

V. Rejections under 35 U.S.C. § 112, first paragraph, enablement of ATCC Deposit Number 209580

Claims 44-58 were rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. *See* Paper No. 8, page 10, lines 3-7.

Applicants point out that the disclosure regarding the ATCC Deposit Numbers of SEQ ID NOS:X on page 3, lines 1-8 of the specification discloses the name and address of the deposit repository, and states that the deposit was made under the terms of the Budapest Treaty. Furthermore, the accession number the deposits containing the cDNAs corresponding to each gene/clone of the present application is listed in Table 1, which appears on pages 93-97 of the specification. Furthermore, for each gene/clone and ATCC deposit, this table lists essential identifying characteristics, such as the length of the cDNA insert and the position of the 5' nucleotide of the predicted open reading frame. Thus, the deposited materials are sufficiently describd to allow specific identification.

With regard to the Examiner's statement in Paper No. 8, page 10, lines 13-15, that, "**The specification does not disclose a repeatable process to obtain the biological**

materials and it is not apparent if the biological materials are readily available to the public," (emphasis added) the Applicant respectfully disagrees and asks that the Examiner refer to Examples 1 and 2, specification page 127-129, which describes two approaches for isolating a particular clone of the deposited sample.

With regard to the Examiner's statement in Paper No. 8, page 10, lines 13-15, that, "The specification does not disclose a repeatable process to obtain the biological materials and **it is not apparent if the biological materials are readily available to the public**," (emphasis added) the Applicant's counsel hereby states that Human Genome Sciences, Inc., the assignee of the present application, has deposited biological material under the terms of the Budapest Treaty on the International Recognition of the Deposit of Micro-organisms for the Purposes of Patent Procedure with the following International Depository Authority: American Type Culture Collection (ATCC), 10801 University Boulevard, Manassas, Virginia 20110-2209 (present address). The deposits were made on January 6, 1998 and January 14, 1998, accepted by the ATCC, and given ATCC Accession Numbers 209568 and 209580, respectively. In accordance with M.P.E.P. § 2410.01 and 37 C.F.R. § 1.808, assurance is hereby given that all restrictions on the availability to the public of ATCC Accession Numbers 209568 and 209580 will be irrevocably removed upon the grant of a patent based on the instant application, except as permitted under 37 C.F.R. § 1.808(b).

VI. Rejections under 35 U.S.C. § 112, first paragraph, New Matter Rejection

Claims 30, 34 and 47 were rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. More particularly, on page 12, lines 2-8, Paper No. 8, the Examiner states the following:

> The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a **New Matter** rejection. Support for "human antibody", recited in claims 30 and 47; and luminescent label and bioluminescent label, recited in claim 34, is not found within the specification, as originally filed.
>
> *Applicant is required to cancel the **New Matter** in the response to this Office Action.* Alternatively, Applicant is invited to clearly point out the written support for the instant limitations.

With regard to the rejection of claims 30 and 47 directed toward "human antibody,"

Applicants respectfully submit that the present specification provides written support for creating human monoclonal antibodies by immunizing an animal, such as a human, with a polypeptide or polypeptide-expressing cell:

> In the most preferred method, the antibodies of the present invention are monoclonal antibodies (or protein binding fragments thereof). Such monoclonal antibodies can be prepared using hybridoma technology. (Köhler et al., Nature 256:495 (1975); Köhler et al., Eur. J. Immunol. 6:511 (1976); Köhler et al., Eur. J. Immunol. 6:292 (1976); Hammerling et al., in: Monoclonal Antibodies and T-Cell Hybridomas, Elsevier, N.Y., pp. 563-681 (1981).) In general, such procedures involve immunizing an animal (preferably a mouse) with polypeptide or, more preferably, with a secreted polypeptide-expressing cell. Such cells may be cultured in any suitable tissue culture medium; however, it is preferable to culture cells in Earle's modified Eagle's medium supplemented with 10% fetal bovine serum (inactivated at about 56°C), and supplemented with about 10 g/l of nonessential amino acids, about 1,000 U/ml of penicillin, and about 100 µg/ml of streptomycin.

See page 137, lines 28-37 of the present specification.

Furthermore, a technique for generating human monoclonal antibody producing B cell lines by Epstein-Barr Virus transformation of B cells collected from an immunized individual was well known in the art at the time. This technique is described, for example, in the 1991 Current Protocols in Immunology procedure entitled "Generation of Epstein-Barr Virus (EBV)- Immortalized B Cell Lines," submitted herewith as Exhibit B; as well as the 1984 publication, "The use of Epstein-Barr virus transformation for the production of human monoclonal antibodies, submitted herewith as Exhibit C; and the 1989 review article, "Strategy for the production of human monoclonal antibodies using in vitro activated B cells," submitted herewith as Exhibit D.

With regard to claim 34, directed to antibodies with a "luminescent label" Applicants respectfully submit that the present specification teaches immunocytochemical or immunohistochemical techniques, i.e. method utilizing labeled antibodies, to detect expression of the polypeptide of this invention in tissue samples:

> Once transgenic animals have been generated, the expression of the recombinant gene may be assayed utilizing standard techniques. Initial screening may be accomplished by Southern blot analysis or PCR techniques to analyze animal tissues to verify that integration of the transgene has taken place. The level of mRNA expression of the transgene in the tissues of the transgenic animals may also be assessed using techniques which include, but are not limited to, Northern blot analysis of tissue samples obtained from the animal, *in situ*

> hybridization analysis, and reverse transcriptase-PCR (rt-PCR). **Samples of transgenic gene-expressing tissue may also be evaluated immunocytochemically or immunohistochemically using antibodies specific for the transgene product.**

See page 160, line 38 to page 161, line 5 of the present specification.

One of skill in the art at the time of filing would have appreciated that immunocytocheimcal or immunohistochemical methods employ labeled antibodies, such as luminescent and bioluminescent labels.

Therefore, claims 30, 34, and 47 are supported by the specification as filed and encompass embodiments that would be recognized and understood by one of ordinary skill in the art, well before the earliest priority date for the present application.

VII. Rejections under 35 U.S.C. § 102

Claims 25-26, 31-40, 44-46, and 48-58 were rejected under 35 U.S.C. 102(b) as being anticipated by Yamada et al. (W094/04563, "Yamada"). The rejection of the claims was based on the language used in U.S. Patent NO. 5,733,549, which is a U.S.C § 371 of PCT/JP93/01142, which is W094/04563, *See,* Paper No. 8, page 12. More specifically, the Examiner states the following:

> Since the antibody that is disclosed by Yamada is known to bind to the amino acid epitope of SEQ ID NO: 125, it is inherent that the same antibody would bind to the same epitope of the protein that is encoded by the HCE5F43 cDNA, which is the nucleotide sequence identified as SEQ ID NO: 55.
> Ergo, Yamada anticipates the claimed invention.

See Paper No. 8, page 14, lines 6-10.

Applicants respectfully disagree and traverse. Regarding the rejection of claims under 35 U.S.C. § 102(b), the M.P.E.P states that:

> "[A] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bos. V. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQD2d 1051, 1053 (Fed. Cir. 1987). "The identical invention must be shown in as complete detail as is contained in the ... claim." *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQD2d 1913, 1920 (Fed. Cir. 1989).

See M.P.E.P., 8th Edition, § 2131 (August 2001).

Anticipation can only be established by a single prior art reference that discloses each and every element of the claimed invention. *See Scripps Clinic & Research Found. v. Genentech, Inc.*, 927 F.2d 1565, 1576, 18 U.S.P.Q.2d 1001, 1010 (Fed. Cir. 1991), *clarified*

on recons., 18 U.S.P.Q.2d 1896 (Fed. Cir. 1991).

In the present case, the Examiner refers to Yamada et. al. which teaches that the amino acid sequences of their invention, such as SEQ ID NO:2, can be used to generate antibodies that specifically recognize lipoprotein (a), a polypeptide involved in cholesterol metabolism (emphasis added):

> **Amino acid sequences** having such characteristic features and peptides including a part or the whole of such amino acid sequences exhibit the same antigenicity as that possessed by lipoprotein (a) and do not have the antigenicity of apolipoprotein (a) or plasminogen. That is, they **have immunogenicity capable of inducing the production of antibodies recognizing lipoprotein (a) specifically** and can combine specifically with antibodies to lipoprotein (a). Thus, they serve to determine antibodies **recognizing lipoprotein (a) specifically** and are hence useful, for example, as immunogens for producing antibodies **recognizing lipoprotein (a) specifically, as standard reference materials in the determination of lipoprotein (a) by an immunological assay technique,** or as ligands in the purification of **antibodies recognizing lipoprotein (a) specifically** by affinity chromatography.

See Yamada et. al., U.S. Patent NO. 5,733,549, column 5, lines 48-63.

As stated by the Examiner on page 13, lines 18-20, "Amino acids 1 -7 of SEQ ID NO: 2 in the Yamada reference are the same as amino acids 129-135 of SEQ ID NO: 125 of the instant invention." However, the Yamada et. al. patent does not teach antibodies that specifically bind to a polypeptide comprising amino acid residues 1 to 272 of SEQ ID NO:125, or a polypeptide comprising at least 30 contiguous amino acids of the complete polypeptide encoded by the HCE5F43 cDNA contained within ATCC Deposit No. 209580, or a polypeptide consisting of the complete polypeptide encoded by the by the HCE5F43 cDNA contained within ATCC Deposit No. 209580, as is taught in claims 25, 39, 44, and 56, and dependent claims 26, 31-38, 40, 45-46, 48-55, and 57-58 of the present application.

Thus, the Examiner has alleged that Applicants claimed invention is not novel by simply isolating one small aspect of the claim and ignoring the fact that Applicants have express claim limitations to SEQ ID NO: 125 and polypeptide comprising at least 30 contiguous amino acids of the complete polypeptide encoded by the HCE5F43 cDNA contained within ATCC Deposit No. 209580.

In effect, the Examiner improperly distilled Applicants claimed invention down to an antibody that recognizes a 7 amino acid region, and has made the assumption that this region

constitutes an antigenic epitope. Applicants respectfully assert that per the M.P.E.P. § 2141.02, this is not the standard. The claimed invention must be viewed as a whole and disregarding other claim limitations is not the proper legal standard upon which a *prima facie* case of anticipation is assessed.

In the absence of an express description of each and every element of the invention in a reference, *i.e.*, where a reference is silent about an asserted inherent characteristic of the claimed invention, inherent anticipation can only be established by showing: (1) that the inherent characteristic must necessarily be present in the prior art reference, and (2) that such characteristic would have to have been recognized by a person of ordinary skill in the art at the time. *See Glaxo Inc. v. Novopharm Ltd.*, 52 F.3d 1043, 1047 34 U.S.P.Q.2d 1565 (Fed. Cir. 1995); *Continental Can Co. USA Inc. v. Monsanto Co.*, 948 F.2d 1264, 20 U.S.P.Q.2d 1746, 1749 (Fed. Cir. 1991); *Mickowski v. Visi-Trak Corp.*, 36 F.Supp.2d 171 (S.D. N.Y. 1999).

With respect to the first required showing, substantial uncertainty regarding the existence of a product in the prior art, *i.e.*, uncertainty as to whether the inherent characteristic is inevitably present or necessarily flows from the teaching of the prior art reference, is sufficient to preclude anticipation. *See W.L. Gore v. Garlock, Inc.*, 721 F.2d 1540, 220 U.S.P.Q. 303 (Fed. Cir. 1983); *Bristol-Myers Co. v. USITC*, 69 F.3d 1130, 15 U.S.P.Q.2d 1258 (Fed. Cir. 1989); *In re Oelrich*, 666 F.2d 578, 212 U.S.P.Q. 323 (C.C.P.A. 1981).

While Applicants do not dispute that "Amino acids 1 -7 of SEQ ID NO: 2 in the Yamada reference are the same as amino acids 129-135 of SEQ ID NO: 125 of the instant invention," as stated by the Examiner on page 13, lines 18-20, Applicants submit that one of ordinary skill in the art would be far from certain that the antibodies of Yamada et. al. specifically recognize the shared amino acid residues in the context of a completely unrelated polypeptide, for example, the complete polypeptide encoded by the HCE5F43 cDNA contained within ATCC Deposit No. 209580. For example, it is well known in the art that a protein's three-dimensional structure affects antibody binding because although some proteins may possess similar stretches of primary structures, due to the location of cysteine and hydrophobic residues, different proteins will fold differently, thus affecting epitope presentation and thus, the way an antibody would bind. Therefore, simply because a mere 7 amino acids of a non-homologous protein are the same as the protein of the invention does not necessarily with 100% certainty mean that antibodies raised against SEQ ID NO:2 of Yamada

et. al. would bind to the claimed polypeptides as would be required to properly make a *prima facie* case for inherent anticipation.

Moreover, Applicants note that M.P.E.P. § 2112 instructs that "the fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic." *In re Rijckaert*, 9 F.3d 1531, 1534, 28 U.S.P.Q.2d 1955, 1957 (Fed. Cir. 1993).

Thus, because there is substantial uncertainty as to whether the antibody disclosed by Yamada *et al.* can bind the complete polypeptide encoded by the HCE5F43 cDNA contained within ATCC Deposit No. 209580, this too is sufficient to preclude inherent anticipation.

In conclusion, Applicants submit that for the reasons stated above, the disclosure of Yamada et. al. does not expressly or inherently anticipate antibodies that bind to the claimed polypeptides. Accordingly, Applicants respectfully request withdrawal of the rejection of claims 25-26, 31-40, 44-46, and 48-58 under 35 U.S.C. 102(b).

Conclusion

Applicants respectfully request that the above-made remarks be entered and made of record in the file history of the instant application. The Examiner is invited to call the undersigned at the phone number provided below if any further action by Applicant would expedite the examination of this application. Alternatively, if the Examiner believes that an interview would help resolve any remaining issues, Applicants urge the Examiner to call the undersigned to arrange an interview at their earliest convenience. If there are any fees due in connection with the filing of this paper, please charge the fees to our Deposit Account No. 08-3425. If a fee is required for an extension of time under 37 C.F.R. § 1.136 that is not accounted for above, such an extension is requested and the fee should also be charged to our Deposit Account.

Respectfully submitted,

Date: January 6, 2004

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